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Original Article

Magnetic Resonance Imaging of Hemophilic Joints: Correlations with the Bleeding Phenotype and Physical Examination

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Abstract

Introduction: Blood-induced joint damage as a hallmark of haemophilia continues to occur despite the widespread prophylaxis. Precise assessment and follow-up of joint status are crucial for tailoring their treatment.

Aim: To study the correlation between the bleeding phenotype, the functional joint status, and the magnetic resonance imaging score in pediatric patients with haemophilia.

Materials and methods: Eighty-six joints (ankles, knees, and elbows) in patients aged 10.7±0.5 (range 4 - 20) years with severe/moderate haemophilia A, severe haemophilia B and haemophilia A with inhibitors were included in the study. The joints were assessed by Haemophilia Joint Health Score 2.1 (HJHS2.1) one month after the last hemarthrosis in a non-bleeding state. The magnetic resonance imaging was performed on 40 (46.5%) of the examined hemophilic joints (16 ankles, 11 knees and 13 elbows).

Results: Joint bleeds were present in 37 (38.9%) of the joints with ankles being the most commonly affected. Sixty joints (69.8%) had normal HJHS2.1 score. Only the loss of flexion score differed significantly between the joints and the ankles had highest score. The cumulative number of hemarthrosis in the joint correlated moderately with hemosiderin deposition and strongly with the formation of subchondral cysts on magnetic resonance imaging. The magnetic resonance imaging scores for soft tissue and osteochondral domains correlated moderately with the cumulative number of hemarthrosis in the joint and only with the presence of pain and crepitus of motion from the physical examination.

Conclusions: Magnetic resonance imaging is more sensitive than the bleeding phenotype and physical examination in detecting early signs of haemophilic arthropathy.

Keywords

hemarthrosis, haemophilic joints, haemophilia joint health score, magnetic resonance imaging

INTRODUCTION

Substantial progress has been made in hemophilia care in the last decade. Yet blood-induced joint damage continues to occur. Early detection of this hemophilic arthropathy is crucial for the choice or modification of the treatment approach with the goal to prevent or postpone deterioration of the joint status. A detailed physical examination of the joints is beneficial but not sufficient to identify the early

soft tissue changes. That is why much research has been currently devoted to exploring the diagnostic sensitivity of imaging studies for early hemophilic arthropathy detection and the impact of the identified joint alterations on tailoring the prophylactic treatment.[1-3] The magnetic resonance imaging (MRI) of the six index joints (ankles, knees and elbows) is accepted as the gold standard for depicting the soft tissue and osteochondral changes in haemophilia.[4] Several studies have investigated the correlation between the MRI-detected structural joint alterations and the findings from the physical examination in patients with hemophilia, but the results are controversial.[5-7]

AIM

We aimed here to study the correlation between the bleeding phenotype, the functional joint status, and the MRI score in pediatric patients with hemophilia.

MATERIALS AND METHODS

Eighty-six joints (ankles, knees and elbows) in patients with severe/moderate hemophilia A, severe hemophilia B and hemophilia A with inhibitors were included in the study. The median age of patients with hemophilia was 10.7±0.5 (range 4–20) years. All patients with severe hemophilia A and B received prophylaxis and the single dose of the factor concentrate varied between 16 and 75 UI/kg BW (median 37.8 UI/kg BW). In this cohort, the joints of patients on secondary prophylaxis (38, 40%) and tertiary prophylaxis (12, 12.6%) were prevalent. Primary prophylaxis was initiated for 37 (38.9%) of the joints, and 8 (8.4%) of the joints never received prophylaxis because of inhibitors. All patients received more than 100 exposure doses of factor concentrate until the date of enrolment.

We searched the medical files and patient diaries for information about the age of patients, age at diagnosis of haemophilia, age at first factor concentrate substitution, age at onset of prophylaxis and reaching full-dose prophylaxis, age at the first joint bleed, and cumulative number of bleeds per joint. The annual joint bleeding rate (AJBR) was calculated as a mean ± standard error for the last 3 years.
The joints were assessed by HJHS2.1 one month after the last hemarthrosis in a non-bleeding state. We performed MRI on 40 (46.5%) of the examined hemophilic joints (16 ankles, 11 knees and 13 elbows) in patients between 7 and 19.5 years of age on GE Signa Hdxt-1.5 T field strength. Five measurements in three planes were used for each joint: T2/ MERGE-gradient echo images; T1/ FSE; PD/FS FSE; T2/ FSE and T2/ STIR. No contrast enhancement was applied. The patients did not require sedation for the MRI. The scoring of the images was performed by two board-certified joint MRI radiologists, who were blinded to the history and the physical findings of the patients. The Compatible MRI scale for scoring the hemophilic arthropathy was applied.[8,9]

Statistical analysis

The data were analyzed using SPSS 11.0 (Chicago, Illinois). The level of significance was set at $p<0.05$. Pearson's chi-square and Fisher's exact (or Student t test) tests were used to compare the qualitative variables between groups. Independent T-test or Mann-Whitney U test for non-parametric distribution were applied to compare quantitative variables between two groups and One-Way ANOVA with Bonferroni correction or Kruskal-Wallis H for non-parametric distribution – for more than two groups. The Pearson correlation coefficient (r) was tested and values of 0.1–0.3 were interpreted as weak correlations, between 0.4 and 0.6 were considered moderate and > 0.6 - strong.

RESULTS

Bleeding phenotype

A hemarthrosis was the first hemophilia symptom and a cause for the first dosing of a factor concentrate in 18 (18.9%) of the examined joints. The AJBR in this cohort was 1.83±0.37 (1.09 – 2.57) bleeds per year and did not differ significantly between the joints. Reported joint bleeds were present in 37 (38.9%) of the joints and they were traumatic in 23 (24.2%) of all the joints. The ankles were most commonly affected by reported bleeds. The cumulative number of joint bleeds in the group was 3.83±0.88 hemarthroses per joint. Target joints were 16 (16.9%) of the joints and the right ankle and right elbow were most commonly involved.

HJHS 2.1 score

Sixty joints (69.8%) had normal HJHS score. The total mean joint HJHS score is 1.8±0.37 (0 – 15) points **(Fig. 1)**.

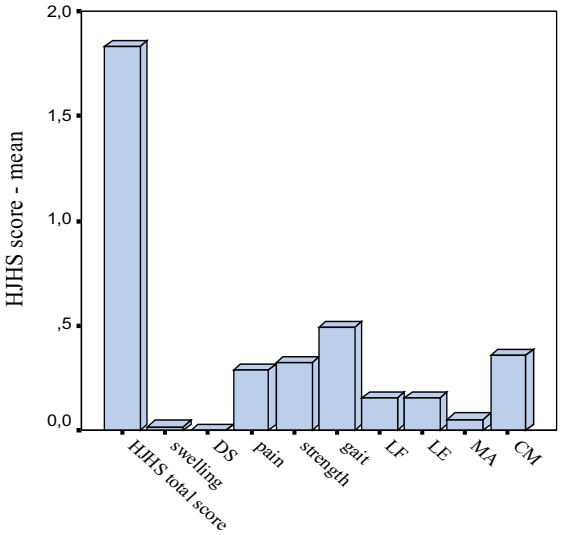

Figure 1. HJHS 2.1 score of the examined joints.
HJHS: haemophilia joint health score; DS: duration of swelling; LF: loss of flexion; LE: loss of extension; MA: muscle atrophy; CM: crepitus of motion

From the separate domains, the global gait changes were prevalent, followed by crepitus of motion and decreased strength. Only the loss of flexion score differed significantly between the joints (F: 2.25; p<0.05) and the ankles had the highest score. There was a moderate correlation between the cumulative number of joint bleeds and the total HJHS score (r: 0.56; p<0.001), joint pain (r: 0.57; p< 0.001), muscle atrophy (r: 0.62; p< 0.001) and crepitus of motion (r: 0.51; p< 0.001). No association was found between the total HJHS score and the AJBR. The total HJHS score was normal in 15 (44.1%) of the joints with reported hemarthroses. On the other hand, we detected abnormal HJHS score in 7 (13.5%) of the joints without history of bleeding. The total HJHS score and the score of the separate HJHS domains was significantly higher in patients older than 10 years, compared to the younger patients (r: 0.47; p< 0.001) and in the group with prophylaxis started after 2 years of age (F: 9.5; p=0.003). The latter association was specifically valid for the domains "pain" (F: 30; p< 0.001), "gait" (F: 45.4; p< 0.001) and "crepitus of motion" (F: 31.4; p<0.001) and weaker for "loss of flexion" (F: 5.2; p< 0.05) and "strength" (F: 6.8; p<0.05).

MRI score

Total MRI score of 0 points (= pristine joints) was found in only 5 (12.2%) of the examined joints. The distribution of the affected joints by site is shown in **Table 1**. Nine (22.5%) of the MRI examined joints were target joints: 5 ankles, 3 elbows and 1 knee.

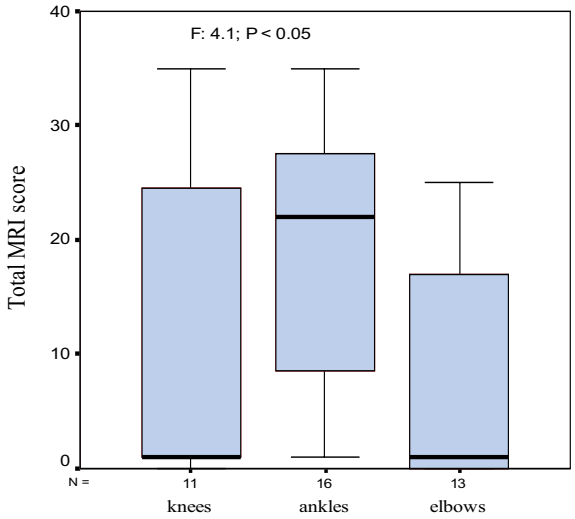

Figure 2. Boxplots of the total MRI score of knees, ankles and elbows.

ges in 21 (51.3%) of the joints, but erosions involving more than 50% of the articular surface were revealed in only 4 (9.8%) of them. Additionally formed subchondral cysts were proven in 7 (17.1%) of the joints.

The total MRI score did not differ significantly between the target joints and the non-target joints. MRI-proven damage was present in 25 (69.4%) of the joints without history of a target joint based on the assessment of the patients/parents. The differences in the scores of the separate MRI domains reached statistical significance only for the hemosiderin detection in the target joints (p=0.018) as an indicator of recent bleeds and the formation of subchondral cysts (p=0.025).

Table 1. Cross tabulation of the joint damage by the scanned joint and the total MRI score

MRI score Joint		Pristine	Damaged	Total
Knees	% of the joints	1 (9.1%)	10 (90.9%)	11 (100%)
	% of the total MRI score	20%	28.6%	27.5%
Ankles	% of the joints	0	16 (100%	16 (100%)
	% of the total MRI score		45.7%	40%
Elbows	% of the joints	4 (30.8%)	9 (69.2%)	13 (100%)
	% of the total MRI score	80%	25.7%	32.5%

The ankle joints in this cohort were most severely affected and their median total MRI score was 19.5±2.8 (13.5 – 25.5) points. The median total MRI score of the knees was 11.9±4.3 (2.1 – 21.6) points. We found the lowest median total MRI score for the elbows: 7.1±2.6 (1.4 – 12.9) points **(Fig. 2)**.

The assessment of the soft tissue and osteochondral MRI domains demonstrated predominantly mild joint changes. In 25 (61%) of the joints mild effusion was detected. No synovial hypertrophy or hemosiderin deposition were found in 22 (53.7%) of the joints. Cartilage changes were present in 20 (48.8%) of the scanned joints, but only in 2 of them there was total cartilage loss. The MRI detected bone chan-

The total MRI score correlated moderately with the cumulative number of joint bleeds (r: 0.48; p=0.001) and AJBR (r: 0.34; p=0.02). MRI-proven joint alterations were present in 12 (33.3%) of the asymptomatic joints without history of bleeds. Synovial hypertrophy was present in 4 (25 %) and osteochondral damage – in 6 (37.5%) of them. No subchondral cysts were detected in the asymptomatic joints. No correlations were shown with the patient's age, age at diagnosis of haemophilia, age at first factor concentrate substitution, age at onset of prophylaxis and rea-

ching full-dose prophylaxis and age at the first joint bleed.

The MRI score for synovial hypertrophy differed significantly between the joints (F: 10.9; $p<0.001$), being highest for the ankles and almost absent for the elbows **(Fig. 3)**. The same difference was valid also for hemosiderin deposition (F: 6.7; $p=0.003$).

The correlation of the separate MRI domains with the bleeding phenotype and the HJHS2.1 score are shown in **Table 2**.

The cumulative number of hemarthroses in the joint correlated moderately with hemosiderin deposition and strongly with formation of subchondral cysts. The AJBR correlated moderately with the presence of synovial hypertrophy and hemosiderin deposition. The MRI scores for soft tissue and osteochondral domains correlated moderately only with the presence of pain and crepitus of motion from the physical examination.

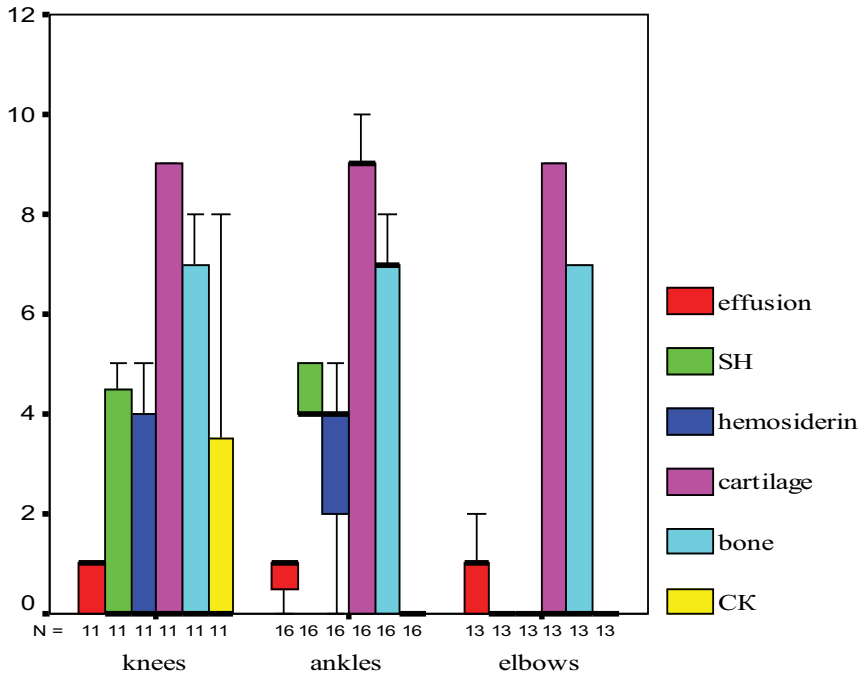

Figure 3. Boxplots of the MRI score for knees, ankles and elbows.

Table 2. Correlation between the MRI score, bleeding phenotype and HJHS2.1

MRI score Variable	Effusion r (*p*)	Synovial hypertrophy r (*p*)	Hemosiderin r (*p*)	Cartilage damage r (*p*)	Bone damage r (*p*)	Subchondral cyst r (*p*)
Age at first joint bleed	0.21 (0.40)	0.19 (0.45)	0.09 (0.71)	0.20 (0.43)	0.20 (0.43)	0.03 (0.90)
AJBR	0.17 (0.28)	0.40 (0.01)	0.41 (0.008)	0.19 (0.21)	0.25 (0.11)	0.35 (0.02)
Cumulative number of bleeds	0.02 (0.9)	0.47 (0.002)	0.49 (<0.001)	0.30 (0.05)	0.34 (0.02)	0.55 (<0.001)
HJHS – total score	0.03 (0.82)	0.41 (0.008)	0.24 (0.12)	0.17 (0.27)	0.17 (0.26)	0.01 (0.95)
HJHS - swelling	0.2 (0.21)	0.13 (0.41)	0.14 (0.37)	0.15 (0.34)	0.16 (0.32)	0.06 (0.68)
HJHS – duration of swelling	-	-	-	-	-	-
HJHS - pain	0.03 (0.81)	0.44 (0.004)	0.37 (0.02)	0.33 (0.03)	0.39 (0.013)	0.10 (0.51)
HJHS – muscle atrophy	-	-	-	-	-	-
HJHS – crepitus of motion	0.07 (0.65)	0.41 (0.008)	0.47 (0.002)	0.44 (0.004)	0.49 (0.001)	0.17 (0.29)
HJHS – loss of flexion	0.01 (0.9)	0.25 (0.10)	0.04 (0.80)	0.08 (0.61)	0.06 (0.97)	0.01 (0.90)
HJHS – loss of extension	0.2 (0.2)	0.13 (0.41)	0.14 (0.37)	0.15 (0.34)	0.16 (0.32)	0.06 (0.68)
HJHS - strength	0.1 (0.52)	0.25 (0.12)	0.05 (0.73)	0.05 (0.75)	0.02 (0.87)	0.15 (0.33)
HJHS – global gait	0.05 (0.79)	0.23 (0.24)	0.16 (0.41)	0.11 (0.55)	0.12 (0.95)	0.14 (0.48)

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DISCUSSION

The hemophilia-specific MRI alterations included in the available scores are joint effusion, synovial hypertrophy, synovial deposition of hemosiderin, cartilage loss and osteochondral changes (erosions, subchondral cysts).[1,2,9] The characteristics of maturing bones in children should be regarded in order to delineate between minimal arthropathic changes and physiological growth models.[10]

We observed only 36.6% of pristine joints on MRI in the study group. Our results are comparable to the results reported in literature for patients with hemophilia in childhood.[11] Most probably the high proportion of MRI detected joint damage results from the prevalence of patients on secondary prophylaxis in which the joint damage could occur before starting regular substitution with factor concentrate. In our cohort, we detect both soft tissue and osteochondral changes in joints without history of bleeds. Generally, mild changes are more often detected by joint MRI.

The relevance of the clinical symptoms for predicting structural damage is debatable in literature. Manco-Johnson et al. reported lack of MRI proven joint damage in some patients with history of many hemarthroses. Suspected polymorphisms in the inflammatory response could be probably responsible.[12,13] On the other hand, some of the patients without reported joint bleeds have joint damage on MRI.[7,12] The role of the subclinical hemorrhages could be suggested as a cause for hemophilic arthropathy in these cases. On the other hand, Ng et al. performed MRI on 60 joints of Patients with hemophilia at 7 – 28 years of age and revealed 100% negative predictive value of the clinical symptoms for synovial hypertrophy in the knees, weak negative predictive value for the ankles and lack of negative predictive value for the elbows.[14] They recommended follow-up of the dominant elbow by MRI. The bleeding phenotype, characterized by AJBR and occurrence of target joint could not precisely predict structural joint damage in our cohort. The AJBR correlated only with the soft tissue early arthropathic changes: synovial hypertrophy and hemosiderin deposition. The cumulative number of joint bleeds appears as the most helpful biomarker for MRI detected hemophilic arthropathy changes from a clinical point of view in the present study. This is confirmed by other authors.[15] These results point out the potential of the joint MRI for comprehensive assessment of the structural damage, resulting from lifelong bleedings and elimination of the artefact changes from a recent hemarthrosis.

The ankles are the most severely affected on MRI, but this was not confirmed by the physical examination in our cohort. Kraft et al. reported soft tissue changes on MRI in 31% of the index joints without history of bleeds and structural damage in 75% of the examined ankles.[6] Oldenburg et al. consider the ankle as an indicator joint for MRI follow up and assessment of the effect of prophylaxis because of the drawbacks of scanning all the index joints.[16]

Such weak to moderate correlations between the MRI findings of hemophilic arthropathy and the physical examination scores, similar to the present study are reported also by other authors.[11-13,16,17] These data could suggest the impact of possible subclinical bleeds on the early structural changes in otherwise asymptomatic joints. On the other hand, Tasbihi et al. reported statistically significant negative correlation between the functional ability and the MRI scores in 25 patients between 11 and 70 years of age and suggested that clinical evaluation could predict structural joint damage.[18] We find only moderate correlation between the total HJHS score and synovial hypertrophy detected by MRI and no correlation with the other MRI domains. The detected by MRI synovial hypertrophy, hemosiderin deposition and cartilage and bone damage correlate moderately only with crepitus of motion and pain from the physical examination. The prevalent mild MRI joint changes in the present cohort probably explain the hurdles for the precise assessment by physical examination.

CONCLUSIONS

MRI is a more sensitive diagnostic tool for early hemophilic arthropathy detection in children on prophylaxis than the bleeding phenotype and physical examination. The prolonged period of functional compensation in childhood could mask the structural damage and result in normal clinical scores. The therapeutic significance of the MRI proven alterations needs further studies.

Author contribution

N.S. did the selection of patients, the physical examination scoring, the statistical analysis, and preparation of the manuscript.
D.D-P and N T-D. performed the MRI examination and scoring.
M.S. and M.B. contributed to the statistical analysis of the data and the preparation of the manuscript, being tutors of the first author.

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Магнитно-резонансная томография гемофильных суставов: корреляция с фенотипом кровотечения и физикальным обследованием

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Резюме

Введение: Гемартроз суставов как признак гемофилии продолжает возникать, несмотря на широко распространённую профилактику. Точная оценка и контроль состояния суставов важны для выработки индивидуального подхода к лечению.

Цель: Изучить корреляцию между геморрагическим фенотипом, функциональным статусом суставов и результатами магнитно-резонансной томографии у педиатрических пациентов с гемофилией.

Материалы и методы: В исследование были включены восемьдесят восемь суставов (колени, лодыжки и локти) пациентов в возрасте 10,7 ± 0,5 (диапазон 4-20) лет с тяжёлой / умеренной гемофилией А, тяжёлой гемофилией В и гемофилией А с ингибиторами. Суставы оценивали по шкале гемофилии в суставах 2,1 (HJHS2.1) через месяц после последнего некровоточащего гемартроза. МРТ выполнена на 40 (46,5%) исследованных гемофильных суставах (16 голеностопных, 11 коленных и 13 локтевых).

Заключение: Кровотечение из суставов было обнаружено в 37 (38.9%) суставах, наиболее часто поражались голеностопные суставы. Шестьдесят суставов (69.8%) имели нормальные результаты по HJHS2.1. Только результаты потери сгибания значительно различались между разными суставами, и у лодыжек был самый высокий балл. Кумулятивное количество гемартрозов в суставах умеренно коррелировало с отложением гемосидерина и сильно с образованием субхондральных кист на магнитно-резонансной томографии. Результаты МРТ мягких тканей и костно-хрящевых областей умеренно коррелировали с кумулятивным количеством гемартрозов в суставе и только с наличием боли и крепитации во время движения при физикальном обследовании. В заключение можно сказать, что магнитно-резонансная томография более чувствительна, чем геморрагический фенотип и физикальное обследование, для выявления ранних признаков гемофильной артропатии.

Ключевые слова

гемартроз, гемофильные суставы, оценка здоровья суставов при гемофилии, магнитно-резонансная томография